REMARKS

In light of the following commentary, applicants respectfully request reconsideration of the present application. Claims 1, 3, 5, 7, 9, 11, 13, 15, and 17 are pending and claims 2, 4, 6, 8, 10, 12, 14, 16 and 18-20 are cancelled.

Formal Drawings

The Examiner has not yet acknowledged the formal drawings filed on August 27, 2001 and is respectfully requested to do so in the next communication.

Rejections Under 35 U.S.C. § 103

The Examiner has maintained a rejection of the pending claims over the combination of Dmitriev *et al.* (Journal of Virology, 1998), Arap *et al.* (Science, 1998), Merchlinsky *et al.* (Virology 1992), and Rixon *et al.* (Journal of General Virology, 1990). Applicants traverse for the following reasons.

In order to establish a *prima facie* case of obviousness, there must be (1) motivation to combine or modify references, (2) a reasonable expectation of success and (3) a teaching or suggestion of all the elements of the claims. The Examiner must be able to argue all three to demonstrate a *prima facie* case.

Regarding the difference of starting material

In accordance with the present invention, the preparation of a fiber mutant adenovirus vector entails the use of a plasmid, as starting material, that has a complete adenovirus genome but for the E1 and E3 regions. See claim 1 (a). In contrast, Dmitriev uses a plasmid having an only fiber-coding region, while Merchlinsky and Rixon use a linear virus genome, not a plasmid.

Accordingly, no reasonable reading of the cited combination could have gleaned a suggestion to use, as starting material, a plasmid that embodies a complete adenovirus genome minus the E1 and E3 regions. Thus, "preparing a plasmid having a complete adenovirus genome except for the E1 and E3 regions," as prescribed in claim 1, is a claimed

feature not taught or suggested by any combination of the references. Without any of the references teaching or suggesting this feature of the claim, this combination of references fails to meet one of the three required prongs for establishing a *prima facie* case of obviousness. Therefore for this reason alone the rejection must fail.

Moreover, in Dmitriev, a modified fiber is first prepared by inserting a foreign peptide-coding DNA into a shuttle vector (*i.e.* a plasmid having only a fiber HI loop-coding region). Next, the modified fiber is cut out from the vector and introduced into the adenovirus genome by homologous recombination using *Escherichia coli* (Bj5183). In this method, it is necessary to undertake a procedure of taking the fiber portion only from the adenovirus genome, introducing the fiber portion into another plasmid to modify it, and then introducing the modifier fiber portion into the adenovirus genome again. Therefore, in contrast to the present invention, the operative procedure is very complicated and time-consuming. No combination of the cited references would remedy this deficiency of Dmitriev.

Merchlinsky and Rixon differ fundamentally from the present invention in that the object to which the foreign peptide-coding DNA is introduced is a linear virus genome. Both Merchlinsky and Rixon prepare virus solutions by transfection of the DNA obtained by ligation to cultured cells. By using this method, however, self-ligation sometimes occurs, or a desired gene is sometimes not ligated to the virus in a proper manner. In most cases, therefore, a virus having a desired gene sequence cannot be obtained.

In sharp contrast, the present invention provides a method for obtaining a clonal recombinant DNA (adenovirus vector) efficiently, in a very short time, because essentially the entire genome of a virus is rescued in the plasmid. Since the cited combination speaks to different constructs and even at cross purposes, the skilled artisan could have had no reasonable expectation of succeeding in this way by some modification of the prior art. Therefore, the combination of these cited references would not establish a reasonable expectation of success. In this respect, therefore, the Examiner has failed to establish a reasonable expectation of success, one of the requirements for a *prima facie* case of obviousness.

Regarding the use of a unique restriction site that is not originally present in adenovirus genome

The Examiner asserts that Dmitriev also introduces a unique restriction site (EcoRV) into the fiber portion and uses the restriction site for insertion of a foreign, peptide-coding DNA. This contention is incorrect, however.

EcoRV is not a unique restriction site, *i.e.*, one originally absent from the adenovirus genome. To the contrary, a total of seven EcoRV sites are present in adenovirus genome. Dmitriev prepares a plasmid to which only a fiber HI loop-coding region is cloned, and he introduces the EcoRV site therein. All one can say is that the EcoRV is unique in the plasmid having only one part (a fiber HI loop-coding region) of the virus genome prepared by Dmitriev . Accordingly, Dmitriev is silent with respect to a unique restriction site that is not present in the adenovirus genome. Again, the cited reference fails to teach or suggest a feature of the presently claimed invention.

The Examiner also asserts that there are several restriction sites that are not originally present in the adenovirus genome, and that these include not only Csp45I and CLaI but also VspI, SwaI, SmiI, PacI, BspDI, CpoIm Ban III, and SrfI, to name a few (Office Action, page 5, lines 6-9). As noted above, however, there are seven sites for VspI (=Ase I), two sites for CpoI, and one site for SmiI(=Swa I) on the adenovirus genome. In addition, SwaI and SmiI recognize the same sequence; hence, they cut the sequence in the same way. Similarly, BspDI, BanIII, and ClaI recognize the same sequence and cut the sequence in the same way.

Accordingly, there is only a limited number of restriction sites that are capable, in principle, of use as a unique site on the adenovirus genome. Moreover, actually employing such sites is itself problematic, a priori. When preparing a recombinant virus, the introduction of restriction sites leads to a change of the structure of the virus and, as a result, the function of the virus per se may be damaged. In contrast, no such problem occurs in the present invention, since only the minimum sequence recognizing ClaI and Csp45I (six bases for ClaI and six bases for Csp45) is introduced.

In the present invention, a foreign peptide-coding DNA is introduced directly into a sequence that encodes a fiber HI loop-coding region (see claim 1, (d)), using Csp45I and/or ClaI, a unique restriction site that is not originally present in the adenovirus genome (claim 1, (b) and (c)). In other words, a one-step in vitro ligation yields an adenovirus vector wherein oligo DNA encoding a polypeptide of interest (RGD, NGD) is inserted into the sequence encoding a fiber HI loop-coding region.

Thus, the claimed invention provides a simplified, remarkably improved approach to constructing the fiber mutant adenovirus. Neither the approach or its surprising results are presaged by any combination of the cited references.

As explained above, Dmitriev does not disclose the introduction of a foreign peptide-coding DNA directly into a fiber HI loop-coding region of an adenovirus genome using a plasmid having a complete virus genome, and using a unique restriction site that is not originally present in the adenovirus genome for such introduction. Arap teaches only that a NGD peptide is more effective for tumor homing; there is no suggestion of introducing into the adenovirus genome an oligo DNA, which codes for a peptide of interest, or of using restriction sites, as recited, for such introduction. Merchlinsky and Rixon teach only that a unique restriction site is used in in vitro ligation of DNA encoding a peptide of interest to a liner virus genome. Neither reference suggests a plasmid having an essentially complete virus genome, as presently recited.

The introduction of unique sites (Csp45I and/or ClaI) into a plasmid that embodies a complete adenovirus genome would not have been suggested by Dmitriev's disclosing that a non-unique EcoRV site is introduced into a plasmid having only one part of an adenovirus genome. No aspect of Arap, Merchlinsky, and/or Rixon compensates for this defect.

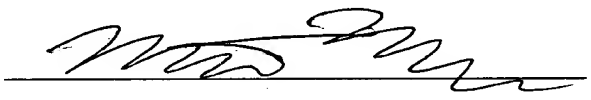
Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The

Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,



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